REMARKS

Status of the Claims

Claims 1-6, 8-12, 14-20, 58-77, 79-88, and 90-92 are pending in the present application. Claims 7 and 13 have been cancelled without prejudice or disclaimer. Claims 15 and 91 have been amended to correct errors in antecedent basis. No new matter has been added by amendment.

The Examiner is respectfully requested to withdraw the rejection and allow claims 1-6, 8-12, 14-20, 58-77, 79-88, and 90-92. In any event, the Examiner is requested to enter the above amendments for purposes of further prosecution. These amendments were not made earlier because Applicants earnestly believe that the specification is enabling for the breadth of the claims as originally drafted.

The Drawings

Upon review of the June 4th Office Action, Applicants noted that Box No. 10 under the Office Action Summary entitled "Application Papers" had been checked to indicate that the drawings filed on 12 October 2001 are objected to by the Examiner. Since no drawings were filed on October 12, 2001, a telephone call was placed to Examiner Li on June 10th to inquire whether or not the drawings rejected were those filed with the application on October 12, 2000 or whether the formal drawings filed on June 12, 2002 were not acceptable. The Examiner stated that since only the Summary Box was checked and no mention of the reason for rejection of the drawings was made in the body of the Office Action, that applicants should assume the June 12, 2002 drawings were acceptable. A check of the Patent Office database indicated that drawings were received and entered into the record on June 12, 2002. The Examiner asked that this be noted in Applicants' response so that she would be reminded to check the file and advise the Applicants if there were problems with the drawings.

The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claim 91 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that it is indefinite for reciting "the method of claim 1" when claim 1 does not recite a method. Claim 91 has been amended to correct this error in antecedent basis, thereby obviating the rejection.

The Rejection Under 35 U.S.C. § 103 Should be Withdrawn

In the final Office Action mailed June 4th, claims 1, 3-11, 13-18, 20, 58-77, 79-88, and 90-92 were rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over U.S. Patent No. 6,221,646 to Dwarki *et al.* in view of Robbins *et al.* (1998) *Pharamcol. Ther.* 80:35-47 and Pittman *et al.* (1993) *Blood* 81:2925-35 as evidenced by Vorachek *et al.* (2000) *J.Biol.Chem.* 275:29031-41. In addition, claim 12 was rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,221,646 to Dwarki *et al.* in view of Robbins *et al.* (1998) *Pharamcol. Ther.* 80:35-47 and Pittman *et al.* (1993) *Blood* 81:2925-35 in further view of U.S. Patent No. 5,744,326 to Ill *et al.* Finally, the rejection of claims 2 and 19 under 35 U.S.C. § 103 was maintained on the grounds that these claims were unpatentable over U.S. Patent No. 6,221,646 to Dwarki *et al.*, Robbins *et al.*, and Pittman *et al.* (1993) *Blood* 81:2925-35 in further view of U.S. Patent No. 6,258,595 to Gao *et al.*

On September 2, 2003, an interview between Examiner Li, Examiner Wehbe' and Applicants' and licensee's representatives was conducted to discuss the rejection under 35 U.S.C. § 103. A summary of this interview accompanies the present response. In the interview, Applicants presented the reasons that the rejections under 35 U.S.C. § 103(a) were traversed, and Examiner Wehbe' suggested that Applicants' remarks in response to the office action should focus on the teachings of Dwarki *et al.* with respect the function of the ITR in AAV vectors, and on the statements in the Zhang *et al.* reference that teach away from using an ITR to drive transcription of a transgene.

U.S. Patent No. 6,221,646 (Dwarki *et al.*) describes rAAV vectors having a heterologous gene positioned between two ITRs. In every embodiment, these vectors contain a promoter other than the ITR that drives expression of the heterologous gene. See, for example, lines 27-39 of column 6 and lines 50-64 of column 8. The patent teaches the use of an enhancer in an rAAV

vector, but only in conjunction with a heterologous promoter. See, for example, lines 34-37 of column 6. While the patent suggests that vectors could be used to express full-length factor VIII, the teaching is only for expressing factor VIII with a promoter other than the ITR. Thus the '646 patent does not teach or suggest an rAAV vector having an ITR as the only promoter driving expression of B-domain deleted factor VIII.

Robbins *et al.* teaches that one disadvantage of using AAV vectors for gene therapy is that vectors larger than 5.2 kb are not efficiently packaged, and thus AAV can only be used for transfer of inserts smaller than 5 kb. *See*, Robbins *et al.*, page 40, column 2. The Robbins *et al.* reference does not teach or suggest constructing an rAAV vector having an ITR as the only promoter driving expression of B-domain deleted factor VIII.

Pittman *et al.* teach the sequence and properties of a B-domain deleted factor VIII protein. The authors state that their goal for producing B-domain deleted factor VIII was to generate a smaller factor VIII molecule that could be expressed more efficiently and that would have reduced heterogeneity. The authors suggest that B-domain deleted factor VIII may be useful in gene therapy, but they do not teach or suggest the use of AAV vectors for expressing B-domain deleted factor VIII, nor do they teach or suggest the construction of an rAAV vector for expression of B-domain deleted factor VIII having an ITR as the only promoter driving expression of a nucleotide sequence encoding B-domain deleted factor VIIII.

U.S. Patent No. 5,744,326 to Ill *et al.* teaches the use of a viral regulatory sequence to increase expression of intronless genes. The intronless gene is operably linked to a promoter sequence. The patent cites to Goeddel, *Gene Expression Technology: Methods in Enzymology* p. 185, Academic Press, San Diego, CA (1990) for examples of the regulatory sequences in the expression construct. While the patent demonstrates the use of this expression vector to express B-domain deleted factor VIII, the patent does not even contemplate the use of the expression construct in a viral vector. Thus, the patent does not teach or suggest the use of the ITR as the only promoter driving expression.

U.S. Patent No. 6,258,595 to Gao *et al.* describes an rAAV vector comprising a spacer sequence interposed between the promoter and the rep gene ATG start site. This reference clearly teaches the use of a promoter other than the ITR to drive expression of the coding

sequences contained in the rAAV vector. See, for example, lines 22-62 of column 5. Accordingly, this reference does not teach or suggest the construction of an rAAV vector containing a spacer and an ITR, where the ITR is the only promoter driving transcription of a heterologous nucleotide sequence.

In the rejection under 35 U.S.C. § 103(a), the Examiner also discusses Zhang *et al.* (1998) *Proc. Natl. Acad. Sci. USA* 95:10158-63, which was cited by the Applicants in the Amendment mailed March 11, 2003. As discussed in the interview on September 2, Zhang *et al.* describe the use of an AAV ITR as the only promoter to express CFTR, but also teach that very low levels of expression are obtained when the ITR is the only promoter driving transcription. See, lines 8-11 of column 1 on page 10159. The reference is directed to determining the regions of the CFTR gene that may be deleted to make room for a more efficient promoter. Figure 3 of this reference shows a comparison of the CFTR expression levels obtained using an AAV ITR and the AAV p5 promoter to drive expression and illustrates that the AAV ITR is a very inefficient promoter in comparison with the p5 promoter. Accordingly, this reference teaches away from using the AAV ITR as the only promoter driving expression of a transgene, and does not teach or suggest that the use of the ITR with an enhancer in an AAV vector for the expression of B-domain deleted factor VIII.

Even if considered together, the cited references do not provide a suggestion or motivation to those of ordinary skill in the art to make the compositions of claims 1-6, 8-12, 14-20, 58-77, 79-88, and 90-92. The '646 patent teaches an AAV vector containing a heterologous gene positioned between two AAV ITRs, but states that the purpose of the ITRs is to allow for replication and packaging of the AAV vectors. The patent suggests that Factor VIII may be expressed using the described AAV vectors, but does not discuss the fact that an AAV vector containing a sequence encoding full-length Factor VIII would be too large to be packaged into AAV virions. Pittman *et al.*, merely teach B-domain deleted factor VIII. Robbins *et al.* recognizes the problem that is solved by the present invention, i.e. that the packaging size limitation of AAV vectors limits their use for the expression of larger coding sequence. However, the Robbins *et al.* does not suggest any solution to this problem.

Accordingly, the combination of references provides no motivation or suggestion to combine the AAV ITR with the B-domain deleted factor VIII sequence taught by Pittman *et al.* to make an AAV vector having a sequence encoding B-domain deleted factor VIII, where the only promoter driving expression of the sequence encoding B-domain deleted factor VIII is the AAV ITR.

In the present case, no *prima facie* case of obviousness has been established because the art cited in the Office Action does not suggest the desirability of using an AAV ITR and an enhancer to drive transcription of a sequence encoding B-domain deleted factor VIII, where the AAV ITR is the only promoter driving transcription of the AAV ITR. In fact, the prior art teaches away from such a combination. For example, Dwarki *et al.* teach that AAV ITRs are included in the AAV vectors because they are required for DNA replication and packaging of the virion. Zhang *et al.* teach that the AAV ITR is a very weak promoter and teach that a strong conventional promoter should be used to drive transcription of a transgene.

Furthermore, as described on page 17 of Applicants' Amendment mailed March 11, 2003, the prior art teaches that expression of factor VIII is difficult because the message is poorly translated and the protein is inefficiently transported to the endoplasmic reticulum and is subject to proteolytic degradation in the blood stream. As a result, efficient transcription of a factor VIII transgene is required to give useful levels of factor VIII protein.

Accordingly, even if the prior art is considered together, it does not teach or suggest the construction of an rAAV vector with a nucleotide sequence encoding B-domain deleted factor VIII operably linked to an AAV ITR and an enhancer, where the AAV ITR is the only promoter driving expression of the nucleotide sequence encoding factor VIII. In fact, it is the Applicants' disclosure is the first to teach the advantage of this combination and provide the motivation and teaching to make such a vector.

As set forth individually below, all grounds for rejection under 35 U.S.C. § 103(a) have been overcome. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 3-11, 13-18, 20, 58-77, 79-88, and 90-92 have been rejected under 35 U.S.C. § 103 on the grounds that they are unpatentable over U.S. Patent 6,221,646 to Dwarki *et al.* in view of Robbins *et al.* and Pittman *et al.* The rejection is respectfully traversed on the grounds that these references fail to teach or suggest all the limitations of these claims. As noted above, Dwarki *et al.* teach the use of a promoter other than an ITR for expression of a transgene in an rAAV vector, and teach that ITRs are present in the rAAV vector to allow for replication and packaging of the vector. Neither Robbins *et al.* nor Pittman *et al.* teach or suggest the use of an ITR as the only promoter driving expression of B-domain deleted factor VIII. Accordingly, these references do not teach or suggest the claim limitations that are deficient in the '646 patent, and it is respectfully submitted that the rejection should be withdrawn.

Claim 12 has been rejected under 35 U.S.C. § 103 on the grounds that it is unpatentable over U.S. Patent No. 6,221,646 to Dwarki *et al.* in view of Robbins *et al.* (1998) *Pharamcol. Ther.* 80:35-47 and Pittman *et al.* (1993) *Blood* 81:2925-35 in further view of U.S. Patent No. 5,744,326 to Ill *et al.* The rejection is respectfully traversed on the grounds that these references fail to teach or suggest all the limitations of this claim. Even if considered with the primary references, the '326 patent fails to teach or suggest the use of rAAV vectors for the expression of B-domain deleted factor and fails to teach or suggest the use of an AAV ITR as the only promoter driving expression of B-domain deleted factor VIII. Accordingly, this reference, even if considered with the primary references cited above, does not teach or suggest the deficiencies noted above for the primary references cited in the rejection, and it is respectfully submitted that the rejection should be withdrawn.

Claims 2 and 19 were rejected under 35 U.S.C. § 103 on the grounds that they are unpatentable over U.S. Patent No. 6,221,646 to Dwarki *et al.*, Robbins *et al.*, and Pittman *et al.*

in further view of U.S. Patent No. 6,258,595 to Gao *et al.* The rejection is respectfully traversed on the grounds that the cited references fail to teach or suggest all the limitations of these claims. Even if considered with the primary references, the '595 patent does not teach or suggest the use of an AAV ITR as the only promoter driving expression of B-domain deleted factor VIII. Accordingly, this reference does not teach or suggest the deficiencies noted above for the primary references cited in the rejection, and it is respectfully submitted that the rejection should be withdrawn.

CONCLUSIONS

It is believed that all the rejections have been obviated or overcome and the claims are in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned agent.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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